REMARKS

The specification has been amended merely to update the priority information.

Claims 2-4 have been canceled by the above amendment. Claims 1, 6 and 8 have been amended and new claims 41-62 have been added. The amended and new claims are supported throughout the application. In particular, claim 1 has been amended to incorporate the limitation of claim 4, now canceled; claim 6 has been rewritten as an independent claim; and claim 8 has been amended to recite specific hybridization conditions as described, e.g., at page 22, lines 1-8. Support for new claims 41-47 can be found, e.g., at page 5, lines 1-5. New claims 48-62 are directed to methods of screening and are dependent from the composition claims currently under examination. These claims are similar to original claims 31-36 (currently withdrawn) and have been rewritten as dependent claims. No new matter has been added.

Claims 1, 5-8 and 28-62 are pending. Claims 28-40 are withdrawn. Claims 1, 5-8 and 41-47 are currently under examination.

Rejoinder

Applicants respectfully request that claims 48-62 be joined in this application once the composition claims currently under examination are deemed allowable, as permitted under M.P.E.P. §821.04. Applicants thank the Examiner for alluding to rejoinder of Group III in the office action at page 2.

Objections to the Specification

As requested by the Examiner, the title of the specification has been amended to better describe the invention, and the priority information has been amended to include U.S. patent information.

Drawings

A transmittal of formal drawings is being filed herewith.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 1-8 are rejected for lack of written description.[1] The Examiner states:

> The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptide sequences set forth in [claims] 1-8.

At the outset, Applicants note that the Examiner acknowledges that the specification "meets the written description and enablement provisions" for SEQ ID NOs:1 and 2 (see page 4 of office action). Thus, according to the Examiner's own reasoning, claims 5 and 6 (and new claims 46-47, which are even more narrowly drawn) should not be rejected. Applicants assume that the rejection of claim 5 and 6 (if such a rejection was intended) was in error and respectfully request withdrawal or clarification of the rejection.

To address the rejection of the remaining claims, Applicants have amended claim 1 to increase the required degree of structural identity to 90%, substantially narrowing the scope of the claim. Claims 2-4 have been canceled. New claims 41-47 are drawn to even narrower embodiments of the claimed polypeptides. The rejection is respectfully traversed insofar as it may be applied to the present claims. The claimed polypeptides are limited structurally in that they have extremely high (at least 90%) sequence identity to a specific reference sequence (claims 1, 44 and 45), have a very limited number of conservative substitutions compared to the reference sequence (claims 7 and 41-43), or are encoded by a DNA that hybridizes under specific stringent conditions to the reference sequence (claim 8). The claimed polypeptides are also quite limited functionally in that they have a specific (and readily assayable) biological activity, namely induction of osteocyte differentiation. The specific structural and functional limitations of the claims substantially limit the variation within the genus of the claimed polypeptides.

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[1] On page 4 of the office action, the Examiner says that "claims 1, 3, 9, 11 and 12" are rejected for lack of written description. However, in discussing this rejection, the Examiner repeatedly refers to rejection of claims 1-8. Given that claims 9-27 were previously canceled and only claims 1-8 were under examination, Applicants assume that the Examiner intended the rejection to apply to claims 1-8 or some subset of same.

With regard to claim 8 in particular, the Examiner is directed to Example 9 of the Written Description Guidelines Training Materials (the Training Materials), which indicates that claims of a scope comparable to the present claims, supported by a similar disclosure, meet the written description requirement. In particular, Example 9 of the Training Materials concludes that:

> a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

Example 9 concludes that written description is adequate even though the specification discloses only a single species that falls within the claims. A similar conclusion is reached in Example 14 of the Training Materials, where the claimed polypeptide is defined by its high percent of identity to a single disclosed reference sequence, combined with a biological function (as is the case with present claims 1, 44 and 45 as well as claims 7 and 41-43). The Examiner is reminded that the Federal Circuit, in Enzo Biochem, Inc. v. Gen-Probe Inc. (296 F.3d 1316, Fed. Cir. 2002), has taken judicial notice of the Written Description Guidelines and the Training Materials, and found them persuasive. Accordingly, under the PTO's own Guidelines and Training Materials, and under Federal Circuit law, the claims meet the written description requirement.

In view of the foregoing, Applicants request that the rejection be withdrawn.

Enablement

Claims 1-8 are rejected as allegedly not enabled.[2] As discussed above, the Examiner has acknowledged that claims 5 and 6 are enabled. Accordingly, claims 5 and 6 (and new claims 46-47, which are even more narrowly drawn) should not be rejected. Applicants assume that the rejection of claim 5 and 6 (if such a rejection was intended) was in error and respectfully request withdrawal or clarification of the rejection.

The Examiner provides the following grounds for the rejection:

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[2] Again, Applicants assume that the Examiner meant to reject claims 1-8 (as indicated on page 8, first full paragraph of the office action) and have addressed the rejection accordingly.

> Despite knowledge in the art for producing homologues of a given protein with nucleotide deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function of the protein. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. . . Therefore, predicting which homologues would retain the functions of the protein is well outside the realm of routine experimentation. (Office action, paragraph bridging pages 7-8.)

Claim 2-4 have been canceled. Claim 1 has been substantially narrowed to recite at least 90% sequence identity to the reference sequence. New claims 41-47 are drawn to even narrower embodiments of the claimed polypeptides. This rejection is respectfully traversed insofar as it may be applied to the presently amended claims.

Contrary to the Examiner's statements, it is simply not true that "detailed information regarding the structural and functional requirements of the disclosed protein is lacking." Applicants provide ample guidance regarding the structure and function of the 7F4 protein (SEQ ID NO:1 and 2) and the changes and modification that can be made to the protein while retaining function. For example, Applicants identify the 7F4 protein as a member of the TNF receptor (TNFR) superfamily, a well-characterized group of type 1-membrane proteins containing characteristic cysteine-rich repeats in the extracellular domain. The identity and location of conserved residues and divergent residues between 7F4 protein and mouse TNF receptor are shown in Figure 2. Further structural comparison of the 7F4 protein to other members of the TNFR superfamily is provided in Figure 6. An ordinary skilled artisan could readily use this information, coupled with the knowledge in the art, to determine what residues of the polypeptides can tolerate changes while still retaining the ability to induce osteocyte differentiation. For example, an ordinary skilled artisan would predict that the cysteine rich repeats and other conserved residues shown in Figures 1 and 2 are important for biological activity. In addition, Example 8 provides a routine assay for determining whether a polypeptide induces osteocyte differentiation utilizing KUSA osteoblast cells. The assay involves transfection of osteoblast KUSA cells with a polypeptide. Transfection with a polypeptide of the

invention causes differentiation of the KUSA cells. Such an assay can be performed by routine methods in a high throughput format.

A balancing of the Wands factors in the present case supports enablement. The claims, as presently amended, are narrow, being directed to polypeptides having a very high degree of structural similarity to the reference sequence and a specific, readily assayable biological activity. As the Examiner acknowledges, the knowledge and skill in the art for producing the claimed polypeptides is high. The specification provides a working example and substantial guidance on how to identify polypeptides that have the recited activity. With regard to the quantity of experimentation needed, MPEP §2164.01 provides that "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Similarly, the fact that some time and expense may be required does not necessarily make the experimentation undue. In *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989) (see also MPEP §2164.06), the requirement of approximately $50,000 and 6-12 months of experimentation was not undue experimentation where the application disclosed one embodiment and a method to determine other embodiments, similar to the instant case. In the present case, making and testing the claimed polypeptides would employ only molecular and cell biology techniques disclosed in the specification and routinely practiced in the art.

With regard to the level of predictability in the art, Applicants submit that the situation is not as dire as the Examiner suggests. Indeed, while it is surely true that in some instances a modification, such as a conservative substitution, can affect the function of a polypeptide, it also recognized in the art that, for any given protein, many residues can be substituted without affecting the protein's function. Bowie et al. (1990) "Deciphering the message in protein sequences: tolerance to amino acid substitutions," *Science* 247:1306-1310 (copy enclosed) teaches that "proteins are surprisingly tolerant of amino acid substitutions". Bowie cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (Bowie at page 1306, col. 2, lines 14-17). Presumably the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based

on Bowie et al.'s teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity. Where, as here, one would know to avoid certain types of substitutions in conserved regions, the chances of accidentally abolishing activity with a given substitution is even lower than in the random study described by Bowie et al.

Moreover, Applicants note that the Examiner's argument seems to be focusing on the "unpredictability" factor of Wands to the exclusion of the other factors. Wands requires a balancing of all the factors. On balance, given the specific limitations recited in the claims, the high level of skill in the art, the detailed guidance provided by Applicants, the disclosure of a working example, and the routine nature of any experimentation that might be required to make and use the claimed polypeptides, the present claims are clearly enabled.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8 are rejected as allegedly indefinite. Although the Examiner has rejected claims 1-8 under this section, Applicants note that no grounds for rejection of any of claims 1-6 have been provided. Thus, Applicants respectfully request clarification or withdrawal of the rejection with regard to claims 1-6.

In one aspect of the rejection, claim 8 is rejected as indefinite in the recitation of "stringent conditions." This rejection has been met by amending the claim to recite specific hybridization conditions, as suggested by the Examiner.

In another aspect, claim 7 is rejected as indefinite in its recitation of "conservative substitution." The Examiner asserts that the term "is a relative recitation in that a number of properties could be conserved with amino acid substitution." These grounds for rejection are respectfully traversed. The term "conservative substitutions" is a term of art easily understood by an skilled artisan. Moreover, the term is explicitly defined in the specification at page 21, lines 1-14. The definition provides a list of amino acids that can be conservatively substituted within each family of amino acids. Accordingly, the term would be clear to a skilled artisan in light of the specification.

In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.